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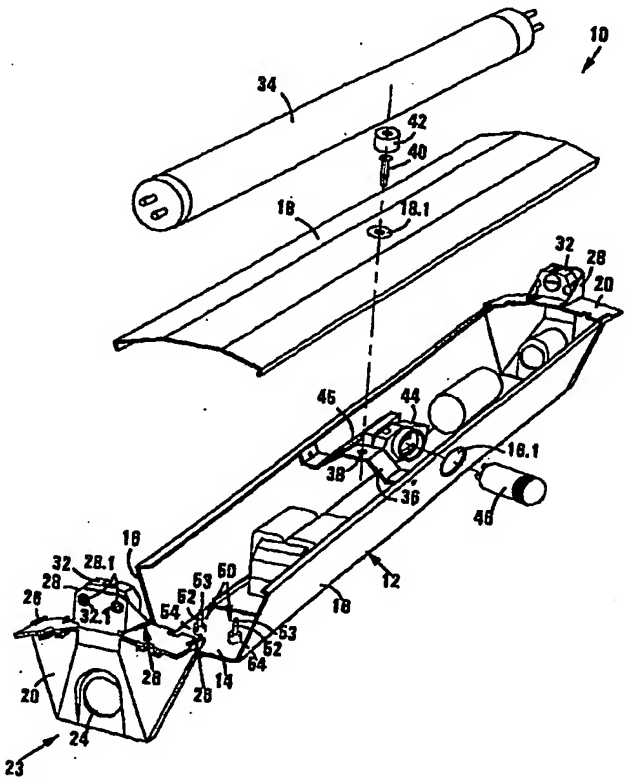
(57) Abstract

The present invention relates to the use of a selective membrane (3) in a biomedical device (1) for the extracorporeal ozonization of blood and biological fluids. The device (1) used in the treatment comprises a hollow body (2) in which there are two compartments (blood compartment: 4") for the passage of two fluids; the compartments are separated by a membrane (3) which is made of polymeric resin for the selective molecular diffusion of ozone and/or oxygen and is substantially inert with respect to ozone.



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USE OF A SELECTIVE MEMBRANE IN A BIOMEDICAL DEVICE FOR THE EXTRACORPOREAL TREATMENT OF BLOOD AND OTHER ORGANIC FLUIDS

TECHNICAL FIELD

The present invention relates to the use of a selective membrane in a biomedical device for the treatment of blood and biological fluids.

In particular, the present invention relates to a biomedical device for the extracorporeal ozonization of blood or biological fluids and to the use of particular membranes in blood treatments performed outside the body.

BACKGROUND ART

Ozone, the active principle used in the present invention, is an unstable gas currently applied as a whitening, oxidizing, and water purifying agent thanks to its disinfectant activity.

In the medical field, during the last few decades ozone has found different applications, from the disinfection of deep wounds of the limbs to the treatment of immune deficiencies and chronic obstructive vasculopathies.

In particular, the validity of the administration of ozone in the treatment of various disorders is currently acknowledged by using it in a mixture with oxygen and by applying it with different administration methods, which include:

-- the intravenous pathway, which provides for the injection of ozone/oxygen mixtures of up to 180 cc per day. This method of administration is currently being abandoned because of the severe pulmonary complications observed in a high percentage of treated cases;

-- the intra-arterial pathway (femoral artery), which provides for the injection of up to 5 cc of O_2/O_3 (30-40 μg/cc). This method of administration associated with autohemotherapy is currently the treatment of election for chronic obstructive vasculopathies and allows to avoid 40% of amputations in stage IV of arteriopathies of the lower limbs;

-- the subcutaneous and intramuscular pathway, which provides for the injection of up to 150 cc of O_2/O_3 (20-40 μg/cc). This method of administration has the drawbacks of being painful during the first minutes, of possibly causing embolization of the patient and of having mediocre patient compliance;

-- the intracavitary (intra-articular, peritoneal and pleural) pathway, which yields positive but anecdotal results;

-- the rectal pathway, by using a Teflon sound. Administration provides for the rectocolonic insufflation of 450-750 cc of gas (20-30 μg) for treating AIDS-related diarrhea, modest rectocolitis and chronic hepatitis. The main drawback of this form of administration is the empirical nature of the dosage, which does not allow to adjust the treatment dose with respect to the actual requirements of the patient;

-- the cutaneous or mucosal pathway, which provides for the treatment of the affected area, delimited hermetically beforehand with a containment bag, with a constant flow of O_2/O_3 (up to 80 μg/cc) for approximately 20 minutes, preventing the patient from inhaling O_3. This procedure, especially if associated with autohemotherapy, is highly effective in the curing of chronic ulcerations of the lower limbs such as bedsores, venous and arterial vasculopathies, gangrenous injuries;

-- IV reinfusion of the blood of the donor, treated ex vivo with O_2/O_3. This technique, known as autohemotherapy, consists in the ex vivo exposure of human blood to a mixture of ozone and oxygen for a short period of time, thus inducing an oxidative stress. The treated blood is then reinfused to the patient. The autohemotransfusion procedure has proved itself adequately safe, relatively low in cost and capable of justifying its use in various disorders.

This procedure, however, is not devoid of drawbacks in use, mainly due to the duration of the treatment, which entails withdrawal of a modest amount of blood (approximately 200-300 ml), insufflation of the mixture

based on oxygen and ozone and/or hydrogen peroxide, and subsequent reinfusion of the treated pouch.

Moreover, another drawback observed in autohemoperfusion is constituted by the impossibility to treat large volumes of blood or derivatives thereof in order to avoid drawing too much blood from the patient.

DISCLOSURE OF THE INVENTION

One of the aims of the present invention consists in avoiding or substantially attenuating the drawbacks observed in the prior art related to the extracorporeal ozonization of blood or biological fluids.

A principal object of the invention is to provide new uses for selective membranes in the field of extracorporeal treatments for the ozonization of blood, plasma or other biological fluids.

Another object of the present invention is to provide a biomedical device for the ozonization of blood or biological liquids allowing to perform an extracorporeal treatment on the entire blood volume in a short time and with a wide safety margin for the patient.

Another object of the present invention is to provide a biomedical device for the ozonization of human blood limiting the risks of embolism that occur in the direct insufflation of the mixture of gases into the circulatory system or into body tissues.

Another object of the invention is to provide a biomedical device for the extracorporeal ozonization of human blood or body liquids which can be manufactured with low production costs.

In view of these and other aims which will become apparent hereinafter there is provided, according to a first aspect of the present invention, the use of a membrane of polymeric resin which is permeable to ozone by molecular diffusion and is substantially inert with respect to ozone in the extracorporeal ozonization of blood or of a biological liquid.

The membranes used in the scope of the present invention are

membranes made of a polymeric resin which is resistant to the oxidative processes caused by contact with ozone and is selectively permeable to ozone or to a gas mixture containing ozone. The passage of the ozone gas occurs through the membranes by molecular diffusion according to the gas concentration gradient.

Particularly adapted polymeric resins are selected from the group that comprises resins of polyethylene, polyurethane, silicone, and combinations of layers of polyethylene/polyurethane/polyethylene resins.

From a structural point of view, the membranes used are hollow-fiber membranes or flat membranes.

Adapted hollow-fiber membranes are constituted by microporous capillaries having a thickness preferably between 40 and 60 μ and an average pore diameter preferably between 0.05 and 0.3 μ.

The microporosity of the membranes prevents the gas from passing in the form of microbubbles (microembolisms), which would damage plasma proteins.

Adapted flat membranes are non-microporous membranes preferably made of silicone with a thickness which is advantageously between 5 and 100 μ. Gas exchange through this type of membrane occurs by molecular diffusion and is proportional to the thickness of the membrane and to the gradient of concentration of the ventilated gas mixture.

Particularly adapted hollow-fiber membranes have a polyethylene content between 40 and 50%, more preferably equal to 45%, and a residual content of soy/castor oil of preferably less than 100 ppm.

In accordance with another aspect of the present invention, a biomedical device for the extracorporeal ozonization of blood and biological liquids is provided which comprises a hollow body in which there are two compartments for the passage of two fluids, these compartments being separated by a selective membrane, the device being characterized in that the selective membrane comprises at least one portion made of a polymeric

resin which is permeable to ozone by molecular diffusion and is substantially inert with respect to ozone.

The Applicant has now found that it is possible to obviate the drawbacks of the prior art observed in the reinfusion of blood with mixtures of oxygen and ozone by supplying one of the compartments of the device of the above-described type with blood or other biological fluid and the other compartment with ozone or a gas mixture containing ozone, so as to provide the transfer of the ozone from the compartment at high concentration to the compartment at lower concentration by molecular diffusion through the selective membrane.

The device according to the invention is provided with membranes of the hollow-fiber or flat-fiber type as described above.

In the device according to the invention, the ozone is preferably administered in a gaseous mixture with one or more physiologically tolerable gases, oxygen being the preferred one among these gases. The mixture of ozone is supplied at a pressure which is preferably between 0.1 and 0.3 bar.

The therapeutic concentration of O_3 in the gaseous mixture is advantageously between 5 and 40 μg/ml. It has been observed that the use of ozone at these levels of concentration facilitates the formation of ROS (reactive oxygen species), natural substances which activate different biological functions.

Moreover, ozone, as a strong oxidizing agent, can regulate the production of antioxidant intracellular enzymes, inhibiting the constant cellular oxidative stress that usually causes degenerative and aging-related disorders.

Another aspect of the present invention relates to the use of a device of the type described above in a method for the extracorporeal ozonization of blood, plasma or biological fluids.

During the use of the device according to the invention, an

extracorporeal stream of blood is pumped into one of the two compartments, while a gas mixture containing ozone is insufflated into the other compartment. The two streams of fluid advantageously flow in countercurrent.

For example, a stream of blood with a flow-rate of 100 ml/min and a stream of O_2/O_3 (O_3 concentration = 30 μg/ml) are circulated in countercurrent in an ozonization device in which the microporous membrane is constituted by a bundle of hollow polyethylene fibers.

This operating method allows to process, in approximately one hour, a volume of blood which is equivalent to the entire blood volume of a patient, while obviating the risks of embolism that occur with methods that provide for the direct insufflation of the mixture of gas into the circulatory system.

Ozonization of the blood of the patient occurs by molecular diffusion of the oxygen/ozone mixture through the selective membrane.

BRIEF DESCRIPTION OF THE DRAWINGS

Further characteristics and advantages will become apparent from the description of a preferred but not exclusive embodiment of a biomedical device for the extracorporeal ozonization of blood and biological fluids, illustrated only by way of non-limitative example with the aid of the accompanying drawing, which is a transverse sectional view of the device according to the invention.

WAYS OF CARRYING OUT THE INVENTION

With reference to the above-cited figure, a biomedical device 1 for the ozonization of blood or plasma is illustrated which comprises a substantially cylindrical hollow body 2 inside which there is, in a substantially longitudinal position, a microporous membrane 3 of the hollow (capillary) fiber polyethylene type, which has an elongated shape and is fixed proximate to the ends 6 and 7 of the body 2 by poured polyurethane resin 15. The microporous membrane 3 is constituted by a bundle of polymeric (polyethylene) microporous capillary fibers which allow the molecular

diffusion of the ozone towards the blood that flows in the adjacent flow compartment 4. The blood flow compartment 4 is delimited by the internal walls of the hollow body 2 and by the external surface of the capillary fibers 3.

The blood flow compartment 4 is supplied by a sterile cannula 12 which is connected, by means of a supply nozzle 8, to the inlet located at one end of the body of the device. A second cannula 13 for reinfusing the treated blood to the patient is connected by means of a second nozzle 9 which is arranged at the opposite end of the body 2 of the device 1.

The body of the device 1 is further provided with an inlet 10 and with an outlet 11 which are arranged proximate to the two ends for the connection of the microporous hollow fibers 3 to the system for feeding the oxygen/ozone mixture. This system is constituted by a feeder cannula 14 and by a discharge cannula 15 connected by means of nozzles to the body of the device 1.

According to one embodiment, the compartment 4 is provided with one or more collection chambers (not shown), which are preferably provided with paths for connection to the outside.

The blood for supplying the device is drawn intravenously from a patient requiring treatment and is transferred to an extracorporeal treatment system. This system comprises a first sterile cannula for transferring the blood from the withdrawal needle to a feeder pump. A second cannula leads from the pump and connects to the nozzle 10 for feeding the blood flow compartment 4 of the ozonization device 1. At the same time, a mixture of oxygen/ozone is insufflated into the microporous capillaries of the filtering membrane 3, so as to produce a stream of gas which flows inside the ozonization device in countercurrent with respect to the blood stream. The gas mixture for ozonization is administered by connecting, by means of a cannula 14, the delivery valve of a gas bottle (not shown) to the nozzle 10 arranged proximate to the inlet of the filtering membrane. A second cannula 15,

connected to the discharge nozzle 11, conveys the gas that leaves the device to a gas recovery system (not shown). The illustrated extracorporeal treatment facilitates the formation of reactive oxygen species in the treated blood which act as natural activators for a large number of biological functions.

The disclosures in Italian Patent Application No. MI98A002831 from which this application claims priority are incorporated herein by reference.

CLAIMS

1. Use of a membrane made of polymeric resin which is permeable to ozone by molecular diffusion and is substantially inert with respect to ozone in an extracorporeal treatment for the ozonization of blood or of a biological fluid.

2. The use according to claim 1, wherein said polymeric resin is chosen from the group that consists of resins of polyethylene, polyurethane, silicone or adjacent layers of polyethylene/polyurethane/polyethylene resins.

3. The use according to claim 1 or 2, wherein said membranes are hollow-fiber or flat-fiber membranes.

4. The use according to claim 3, wherein said hollow-fiber membranes are microporous capillaries whose thickness is between 40 and 60 μ and whose average pore diameter is preferably between 0.05 and 0.3 μ.

5. The use according to claim 1 or 2, wherein said membranes are flat silicone membranes.

6. The use according to claim 5, wherein said flat membranes have a thickness between 5 and 100 μ.

7. A biomedical device for extracorporeal ozonization of blood and biological fluids, comprising a hollow body in which there are two compartments for the passage of two fluids, said compartments being separated by a selective membrane, characterized in that said selective membrane comprises at least one portion made of a polymeric resin which is permeable to ozone by molecular diffusion and is substantially inert with respect to ozone.

8. The device according to claim 7, characterized in that said selective membrane is constituted by a plurality of microporous hollow fibers.

9. The device according to claim 8, characterized in that said hollow fibers have a pore diameter of 0.05 to 0.3 μ.

10. The device according to claim 8 or 9, characterized in that said

hollow fibers have a thickness of 40 to 60 μ.

11. The device according to any one of claims 2 to 4, characterized in that said hollow fibers are joined in a bundle by means of a polyurethane resin adhesive.

12. The device according to any one of claims 8 to 11, characterized in that said hollow fibers are arranged along the central portion of said hollow body and are fixed, at its ends, by pouring polyurethane resin.

13. The device according to claim 7, characterized in that said polymeric resin is chosen from the group that comprises polyethylene, polyurethane and mixtures thereof.

14. The device according to claim 7, characterized in that said polymeric resin contains 45% polyethylene.

15. The device according to claim 7, characterized in that said polymeric resin is constituted by adjacent layers of polyethylene/ polyurethane/polyethylene resin.

16. The device according to claim 7, characterized in that said selective membrane is a flat membrane.

17. The device according to claim 16, characterized in that said flat membrane has a thickness between 5 and 100 μ.

18. The device according to claim 16 or 17, characterized in that said flat membrane is made of silicone.

19. The device according to any one of claims 16 to 18, characterized in that said flat membrane is shaped like a pouch which is rolled up in a spiral.

20. Use of a device according to claims 7 to 19 for the extracorporeal ozonization of blood, plasma or biological fluids.

21. The use according to claim 20, wherein ozone or a mixture of ozone with other physiologically compatible gases is administered.

22. The use according to claim 21, wherein a gaseous mixture containing ozone at a concentration of 5 to 40 μg/ml is administered.

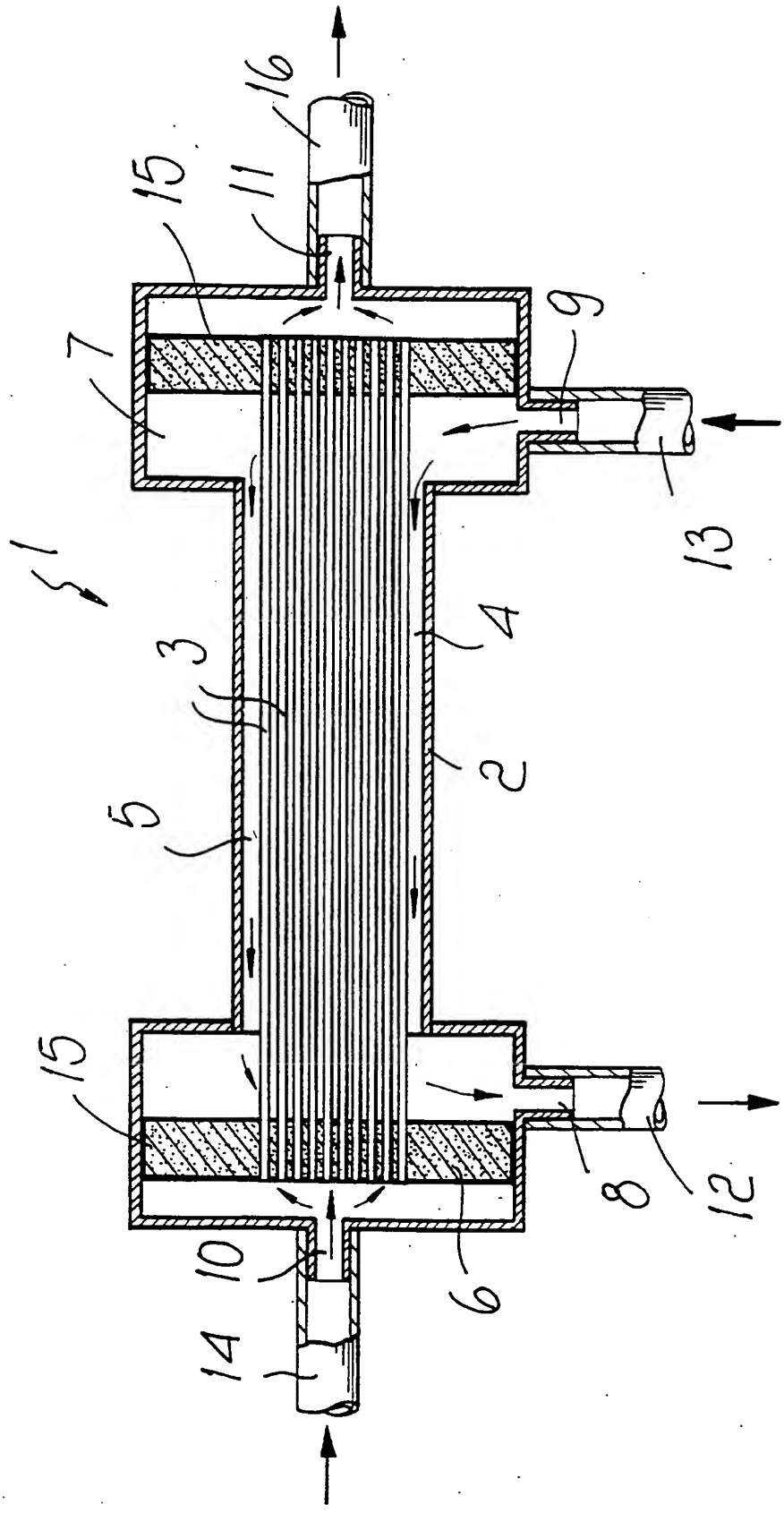
23. The use according to any one of claims 20-23, wherein the ozone is

administered at a pressure between 0.1 and 0.3 bar.

24. The use according to any one of claims 20-23, wherein blood or a biological fluid flows in one compartment and a gaseous mixture comprising ozone flows in the other compartment.

25. The use according to claim 24, characterized in that said gaseous mixture is an O_3/O_2 mixture.

26. The use according to claim 24, wherein the blood or biological liquid and the gaseous mixture containing ozone flow in countercurrent.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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/02041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/16 B01D71/26 B01D71/54 B01D71/70 B01D61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y		2,5,6
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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